

REMARKS

Claims 1-12, 40-56 and 77-92 are now pending in the application. Claims 1-5, 8, 10-12, 40-44, and 47-53 have been amended herein. Claims 13-39 and 57-76 have been cancelled herein. Claims 77-92 have been added herein. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

EXAMINER INTERVIEW

Applicants would like to thank the Examiner and the Primary Examiner for the care taken in examining the claims and for the telephonic interview conducted on Tuesday, December 13, 2005. The pending claims were discussed. During the interview, the Examiner withdrew the rejection under 35 U.S.C. § 102(e) for Claims 1-2, 4-6, 8 and 10-11 as being anticipated by Gordon et al.

AMENDMENT TO SPECIFICATION

Paragraph [0002] has been amended to correctly identify all of the U.S. government support that may have been used for the present inventions. No new subject matter has been added.

REJECTION UNDER 35 U.S.C. § 102

Claims 1-3, 8-9 and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000). This rejection is respectfully

traversed. At the outset, Applicant respectfully submits that the originally filed claims are patentably distinct over the cited reference.

However, in an attempt to expedite prosecution, Applicants have amended Claim 1 to include the step of "providing a plurality of primers designed to hybridize to a first plurality of genes in a tumor sample from the patient" and to include the step of "amplifying said first plurality of genes." Support for this amendment can be found in Table 2, the Sequence Listing, and accompanying text. The primers designed to hybridize to a first plurality of genes are useful for PCR analysis in which the genes are amplified.

In contrast, Alizadeh et al. fails to teach or suggest providing a plurality of primers designed to hybridize to a plurality of genes or amplifying a plurality of genes. For example, Alizadeh et al. analyzes genes by hybridizing the genes to probes on a DNA microarray. DNA microarray analysis does not include the use of primers or the amplification of the genes. Accordingly, reconsideration and withdrawal of the present rejection are respectfully requested.

Claims 1-3, 8 and 10-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Rosenwald et al. (N Engl J Med, vol 346, page 1937-47, June, 2002) or Rocke et al., (US Patent Publication 2002/0111742, August 15, 2002). This rejection is respectfully traversed. At the outset, Applicants respectfully submit that the originally filed claims are patentably distinct over the cited references.

However, in an attempt to expedite prosecution, Applicants have amended Claim 1 as discussed above. In contrast, Rosenwald et al. and Rocke et al. fail to teach or suggest providing a plurality of primers designed to hybridize to a plurality of genes or amplifying a plurality of genes. For example, Rosenwald et al. teaches the use of a molecular profile to

predict survival by examining gene expression with the use of DNA microarrays. As discussed above, DNA microarrays do not use primers or amplify the genes.

Rocke et al. provides a novel method for calculation based on data obtained from DNA microarray analysis and fails to teach or suggest any method for measuring expression in a plurality of genes in a tumor sample. In addition, Rocke et al. fails to teach or suggest providing a plurality of primers designed to hybridize to a plurality of genes or amplifying a plurality of genes. Accordingly, reconsideration and withdrawal of the present rejection are respectfully requested.

Claims 1-2, 4-6, 8, 10-11, 40-41, 43-45 and 49 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Gordon et al., (US Patent Publication 2003/0219760, August 30, 2002). This rejection is respectfully traversed. At the outset, Applicants respectfully submit that the originally filed claims are patentably distinct over the cited reference.

During the interview of December 13, 2005, the Examiner withdrew the rejection for Claims 1-2, 4-6, 8 and 10-11.

In an attempt to expedite prosecution, Claim 40 has been amended to include “the kit comprising a plurality of primers designed to hybridize to the first plurality of genes in the tumor sample from the patient, a database comprising the normalized reference values of the second plurality of genes, and an algorithm for determining which of the at least one of a plurality of classifications groups includes the patient.” Support for this amendment may be found in Tables 2 and 3, the Sequence Listing and accompanying text.

In contrast, Gordon et al. fails to teach or suggest a kit that includes a plurality of primers designed to hybridize to a plurality of genes for the measuring expression of the plurality of genes in a tumor sample from a patient having DLBCL. “The disclosure in

assertively anticipating the reference must provide an enabling disclosure of the desired subject-matter; mirroring or description of the subject-matter is insufficient if it cannot be produced without undue experimentation.” Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). Gordon et al. does not present enabling disclosure for a kit comprising assays for measuring expression of the plurality of genes in a tumor sample from a patient having DLBCL. In contrast, Gordon et al. discloses diagnosing and predicting prognostic molecular markers for mesothelioma, yet not for DLBCL. In addition, Gordon et al. merely discloses a listing of possible genes that may be over-expressed or under-expressed in a DLBCL tumor and does not provide any primer sequences for use with any of the DLBCL-related genes. It would take undue experimentation to enable the disclosure of Gordon et al. by one skilled in the art to provide a kit comprising a plurality of primers designed to hybridize to a plurality of genes in a tumor sample from a patient having DLBCL. Accordingly, reconsideration and withdrawal of the present rejection are respectfully requested.

REJECTION UNDER 35 U.S.C. § 103

Claims 1 and 4-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Rosenwald et al. (N Engl J Med, vol 346, page 1937-47, June, 2002), in view of Gordon et al., (US Patent Publication 2003/0219760, August 30, 2002) and Goldberg et al. (US Patent Publication 2003/0060439, January 11, 2001). This rejection is respectfully traversed. At the outset, Applicants respectfully submit that the originally filed claims are patentably distinct over the cited references.

Rosenwald et al., Gordon et al., and Goldberg et al. do not teach or suggest, either individually or in combination, a method for classifying a patient having DLBCL comprising providing a plurality of primers designed to hybridize to a plurality of genes in a tumor sample and amplifying the plurality of genes. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness as required by *Graham v. John Deere Co.*, 148 USPQ 459 (1966) and MPEP § 2141. Specifically, the following tenets of patent law must be adhered to:

- (A) The claimed invention must be considered as a whole;
- (B) *The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;*
- (C) *The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and*
- (D) Reasonable expectation of success is the standard with which obviousness is determined.

MPEP § 2141.01

There is no teaching, suggestion, or motivation set forth in Rosenwald et al., Gordon et al. or Goldberg et al. to combine these references to produce the claimed invention. “Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in references themselves or in the knowledge generally available to one of ordinary skill in the art.” MPEP § 2143.01 (emphasis added); *In re Fine*, 5 USPQ2d 1596 (Fed Cir 1988). The Examiner is merely attempting to combine the teachings of the cited references to invent the present invention without explicit motivation to combine such teachings. The most recent Office Action is completely silent of any recitation that would direct the Applicants to where such motivation can be found. The Examiner identifies portions of these patents that she relies upon,

but fails to provide citations as to where such motivation to combine these references can be found. More importantly, Applicants are being denied the opportunity to refute such motivation, since none is identified by the Examiner.

It is readily apparent that neither Rosenwald et al., Gordon et al. nor Goldberg et al. provide any teaching, suggestion, or motivation to combine their teachings. Thus, without a teaching, suggestion, or motivation clearly found in within the text of these references, it is improper to combine these references to establish a rejection of obviousness, unless the Examiner can show that such teaching, suggestion, or motivation is generally available in the knowledge of one skilled in the art.

A statement that a modification is well within the skill in the art is not sufficient by itself to establish *prima facie* obviousness. The Examiner simply picks and chooses among these elements that allegedly teach the claimed invention. However, the Examiner has failed to show any motivation within these references to make such a combination.

As appropriately stated in MPEP § 2143.01, “[a] statement that modification of the prior art to meet the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made the references relied upon teach that all aspects of the claimed were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the of the references.” *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)(emphasis in original); MPEP § 2143.01. That is, it is the burden to identify some objective reason to combine the teachings of the references. However, as stated above, the Examiner merely indicated that combinations were “obvious to one of ordinary skill in the art.” Therefore, Applicants respectfully request the Examiner to identify some suggestion or motivation,

either in references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teaching.

Since, at this time, the Examiner has failed to provide any objective evidence found in the references to support the combination of these references, the Examiner must present a convincing line of reasoning as to why one skilled in the art would have combined these references. According to MPEP § 2142, it is the Examiner's initial burden to provide some suggestion of the desirability of doing whatever the inventor has done. Specifically, “[t]o support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

The Examiner is correct in stating that Rosenwald et al. does not teach a method of measuring expression in tumor samples by Real-Time RT-PCR and such statement supports Applicants' discussion of Rosenwald et al. from above. As discussed above, the Examiner has withdrawn her 102(e) rejection in regard to Gordon et al. Gordon et al. fails to provide an enabling disclosure as to RT-PCR for measuring gene expression from a tumor from a patient having DLBCL and one skilled in the art would need undue experimentation to invent the claimed invention. Goldberg et al. alone does not teach a method for classifying a patient having DLBCL as noted by the Examiner. In the absence of any objective evidence or any convincing line of reasoning to combine these references, Applicants respectfully submit that each of the references, either singly or in combination, fail to teach or suggest the claimed invention and,

thus, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, reconsideration and withdrawal of the present rejection are respectfully requested.

Claims 40-52 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gordon et al., (US Patent Publication 2003/0219760, August 30, 2002) in view of by Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000) and Goldberg et al. (US Patent Publication 2003/0060439, January 11, 2001). This rejection is respectfully traversed.

At the outset, Applicants respectfully submit that the originally filed claims are patentably distinct over the cited references. Gordon et al., Alizadeh et al., and Goldberg et al. do not teach or suggest, individually or in combination, the claimed combinations of elements, especially as amended. However, in an attempt to expedite prosecution, Applicants have amended Claim 40 as discussed above.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness as required by *Graham v. John Deere Co.*, 148 USPQ 459 (1966) and MPEP § 2141. Gordon et al. does not provide enabling disclosure as to a kit measuring gene expression of a plurality of genes from a tumor from a patient having DLBCL and one skilled in the art would need undue experimentation to invent the claimed invention as discussed above. Moreover, Alizadeh et al. fails to teach or suggest the use of PCR as a method of classifying patients of having DLBCL as discussed above. Goldberg et al. fails to teach or suggest a kit comprising PCR assays for measuring expression of a plurality of genes from a tumor sample for a patient having DLBCL. In addition, there is no teaching, suggestion, or motivation set forth in Gordon et al., Alizadeh et al., or Goldberg et al. to combine these references to produce the claimed invention. “Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in references themselves or in the knowledge generally available to one of ordinary skill in the art.” MPEP § 2143.01 (emphasis added); *In re Fine*, 5 USPQ2d 1596 (Fed Cir 1988). A statement that a modification is well within the skill in the art is not sufficient by itself to establish *prima facie* obviousness. Accordingly, reconsideration and withdrawal of the present rejection are respectfully requested.

ALLOWABLE SUBJECT MATTER

The Examiner states that claims 53-56 would be allowable if rewritten in independent form. Accordingly, Applicants have amended claims 53-56 to include the limitations of the base claim and any intervening claims. Please note that Claims 51 and 52 were identical as originally filed, therefore, as discussed during the interview on December 13, 2005, the claim limitations of only one of Claims 51 and 52 were added to Claim 53. The scope of Claims 51 and 52 has also been amended. Therefore, claims 53-56 should now be in condition for allowance.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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